REMARKS

Claims 1-15, 18-21 and 75-94 are pending in the instant application.

Claims 16, 17 and 22-74 were previously canceled without prejudice or disclaimer.

Claims 7, 8, 13-19, 75-83 and 91 are cancelled herewith. Claims 1 and 90 are amended.

Support for the amendment to claim 1 can be found, for example, in claims 4-6, 15 and 79 as originally presented and in the specification at Example 5. No new matter has been added.

Applicants reserve the right to pursue to subject matter of the claims as originally presented in one or more continuing applications.

Applicants request reconsideration and withdrawal of the remaining rejections in view of the arguments presented below.

A. Interview Summary

Applicants extend their thanks to the Examiner for his courtesy in conducting a personal interview on September 30, 2009 with Dr. Mario Stevenson and Applicants' representatives, (James Velema and Debra Milasincic) during which the following §103 rejection of record was discussed.

B. Claim Rejections -35 USC §103

The Examiner has again maintained the rejection of claims 1-11, 14, 15, 18-21, 75-84 and 86-94 under 35 U.S.C. § 103(a) for alleged obviousness over Draper et al. (US Patent No. 5,693,535; filed August 13, 1997; granted October 26, 1999) in view of Tuschl et al. (US Patent No. 7,056,704; filed April 27, 2004; granted June 6, 2006). The rejection of claims 12, 13 and 85 under 35 U.S.C. §103(a) over Draper et al. and Tuschl et al. and further in view of Svoboda et al. (Biochem. Biophys. Res. Comm., 287: 1099-1104 (2001)) have also been maintained (see page 4 of Office Action). Specifically, the Examiner maintains that "it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the siRNAs of Tuschl for the ribozymes of Draper when targeting HIV for degradation" (see page 3 of Office Action).

Applicants traverse the rejection and maintain that the skilled artisan at the time of the invention would not have substituted the non-analogous ribozyme art of Draper et al. with the siRNA art of Tuschl et al. in order to arrive at the claimed invention. According to the Examination guidelines set forth by the Office (MPEP 2143, §B), the rationale that a claim is obvious based on the substitution of one known element for another can only be made if the

results of the substitution would have been predictable. Applicants submit that the allegedly simple substitutions relied upon by the Examiner would not have yielded predictable results to one of ordinary skill in the art.

According to the Examiner, "one would have had a reasonable expectation of success" in substituting ribozymes of Draper for the siRNAs of Tuschl "because the target sites of Draper were selected on the basis of their availability for hybridization" (see pg. 6, 1st para. of Office Actoin). Applicants respectfully disagree. Ribozymes are small, self-catalytic RNA molecules which directly hybridize to their targets to mediate cleavage. In contrast, siRNAs are loaded into a macromolecular RISC complex and guide the complex to a target mRNA where the endonuclease activity of the complex mediates cleavage of the target. Due to the much larger size of the siRNA:RISC complex, and its distinct mechanism of action, Applicants submit that one of skill in the art would not have reasonably expected an siRNA to effectively cleave the same target site as a ribozyme.

Not only would the skilled artisan lack a reasonable expectation of success in targeting HIV in general, but Applicants submit that the skilled artisan would have had no reasonable expectation of success in applying siRNA technology to mediate RNA interference (RNAi) of the incoming viral RNA genome of an HIV virus during an early viral replication cycle event. Applicants maintain their position that one of skill in the art would have expected the incoming HIV viral genome to be protected from nucleolytic attack by a siRNA:RISC complex as it is condensed by core proteins that protect it from nucleases and other host cell defense mechanisms (see, e.g., Tanchou et al., *J. Mol. Biol.* (1995), 252:563-567). Indeed, the genomic RNA of other similarly condensed RNA viruses was reported to be resistant to RNAi cleavage (see Bitko and Barik, *BMC Microbiol.*, 1:34-45, (2001), who found that the genomic RNA of RSV is resistant to RNAi cleavage). While Applicants acknowledge that RSV and HIV are not closely related viruses, this does not change the fact that both viruses are tightly associated with nucleoproteins that protect their RNA genomes from nucleolytic attack following entry into an infected cell. Given that both viruses use similar defensive strategies, Applicants' discovery that the HIV genome is actually accessible to siRNA cleavage is highly surprising and unexpected.

Applicants also disagree with the Examiner's statement that "one of ordinary skill in the art would have had reason to believe that HIV genomic RNA was accessible to attack by siRNA" since Sarver et al. (Science, 247:1222-1225, 1990) "showed that ribozymes directed to

HIV gag RNA cleaved 'incoming viral RNA' when expressed in cells that were subsequently challenged with HIV-1" (see paragraph bridging pages 6 and 7of Office Action, emphasis added). Applicants note that the Sarver et al. reference was published almost 15 years before the filing date of the instant application. One of skill in the art at the time of the instant application was filed (2003) would not conclude that the ribozymes of Sarver were in fact capable of cleaving genomic RNA. This is because the data provided by Sarver was generated from total RNA isolated 7 days after infection (see pg. 1224, right col., line 19) and long after the genomic RNA is now known to have been destroyed by the cell.[1]

Nevertheless, even if one would conclude that the ribozymes of Sarver were effective at cleaving incoming genomic RNA, this is no basis for concluding that siRNAs would be similarly effective. As mentioned above, a siRNA-RISC is a much larger complex than a ribozyme, and is far less likely to gain access to the condensed genomic RNA of an RNA virus. As such, the teachings of Sarver are clearly much less relevant to the claimed invention than the teachings of Bitko. One of skill in the art at the time of filing would have been much more inclined to rely on the findings of Bitko (a recent (2001) siRNA reference) than those of Sarver (a 1990 ribozyme reference) in evaluating their expectation of success. Since Bitko demonstrated that the condensed genomic RNA of RSV virus was in fact resistant to siRNA cleavage, one of ordinary skill in the art would have had no reasonable basis for believing that the incoming genomic RNA of HIV could be amenable to attack by siRNA.

At page 8 of the Office Action, the Examiner further states that "even if [the ability of an siRNA to act on condensed viral RNA genome at an early stage] were a surprising and unexpected feature, it would not render the claims non-obvious because it is an inherent characteristic of each and every one of the siRNAs that can target an mRNA or viral genome that is generated from a provirus". The Examiner relies on MPEP 21112(I-II) which states that "something that is old does not become patentable upon the discovery of a new property, and there is no requirement that a person of ordinary skill in the art would have recognized this inherent feature at the time of the invention" (emphasis added).

Applicants respectfully submit the claimed compositions are not known compositions. Indeed, the Examiner has not pointed to any reference which anticipates the claimed

[1] In contrast, Applicants measured the level of HIV genomic RNA within 1 hour of infection (see Figure 2D).

compositions, i.e., isolated siRNAs which are complementary to the gene portion of a HIV portion. That is because the rejection is one of obviousness, not one of inherent anticipation. What is obvious and what is inherent are entirely different questions. See Jones v. Hardy, 727 F.2d 1524, 1529 (Fed. Cir. 1984). While that which may be inherent is not necessarily known, "[o]bviousness cannot be predicated on what is unknown". See MPEP (8th ed.) §2141.02, citing In re Spormann, 363 F.2d 444, 448 (1966). Moreover, in order for an inherent characteristic to render a claim obvious, the inherent characteristic must be known to one skilled in the art at the time the invention was made. See also Kloster Speedstell AB v. Crucible Inc., 793 F.2d 1565, 1576 (Fed. Cir. 1986).

Here the Examiner has predicated the rejection on the assertion that the ability of a siRNA to act on condensed genomic RNA of the HIV virus was a characteristic inherent in isolated siRNAs which target mRNA transcripts expressed at later stages of the HIV life cycle. Yet, contrary to the Examiner's assertion, isolated siRNAs which target later stages of the HIV life cycle were not known or described at the time of the invention. Moreover, such isolated siRNAs were not "obvious siRNAs" because, as mentioned above, one of skill in the art would have no reasonable expectation that isolated siRNAs would be able to cleave viral target sites in the same manner as ribozymes. Accordingly, the fact that the isolated siRNAs of the invention were capable of cleaving incoming genomic RNA is evidence that the invention as a whole was non-obvious and inventive.

Notwithstanding the above, Applicants have canceled claims 17, 8, 13-19, 75-83 and 91 and amended claim 1 without prejudice or disclaimer in an effort to expedite the allowance of the application. As currently amended, claim 1 (and all claims dependent thereon) specify that the isolated siRNA comprises a sequence sufficiently complementary to a HIV genome portion selected from the group consisting of a Long Terminal Repeat (LTR) region, a *nef* gene or portion thereof, and a *vif* gene or portion thereof, and that the siRNA promotes the degradation of genomic viral HIV RNA during an early viral replication cycle event to inhibit synthesis of viral reverse-transcription intermediates and establishment of a HIV provirus.

The claimed *vif*, *nef* and LTR-targeting siRNAs address a long-felt need in the field of HIV therapy: the ability to "sterilize" the cell from a productive infection. Not only have Applicants demonstrated that the presently claimed siRNAs cleave incoming genomic RNA (see Figure 2d) but these siRNAs have been shown to drastically reduce both the synthesis of viral reverse transcription intermediates (see Figure 2e) and the levels of viral integrants (see Figure 2f). Thus, Applicants have demonstrated that the presently claimed siRNAs can effectively prevent establishment of a productive infection by cleaving the few copies of incoming genomic HIV RNA before they can be reverse transcribed to form a HIV provirus that irreversibly integrates into the host cell chromosome. That this result was recognized by those of skill in the art as a surprising, unexpected, and significant scientific breakthrough is reflected in the publication of Applicants' invention in the prestigious scientific journal *Nature*.

In conclusion, Applicants respectfully submit that they have presented ample evidence in support of a finding of non-obviousness. First, Applicants have established that there would be no reasonable expectation of success were one of skill in the art to seriously consider substituting ribozymes with siRNAs in order to mediate RNAi of an HIV genome portion, much less promoting the degradation of complexed genomic viral HIV RNA during an early viral replication cycle. Second, even if it were *prima facie* obvious to substitute ribozyme art for siRNA technology, Applicants have demonstrated the claimed invention provides superior properties or advantages that a person of skill in the art would have found surprising or unexpected. Specifically, Applicants have surprisingly demonstrated that isolated siRNAs which mediate RNAi of LTR, *nef*, or *vif* regions within the HIV genome can prevent the establishment of a productive HIV infection by significantly degrading genomic viral RNA during an early viral replication cycle such that the synthesis of viral reverse-transcription intermediates and the integration of the HIV provirus are inhibited.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) for alleged obviousness be reconsidered and withdrawn.

CONCLUSION

In view of the above amendment and response, Applicants believe the pending application is in condition for allowance. Nevertheless, if a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney, Debra J. Milasincic, Esq., at (617) 227-7400.

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Respectfully submitted,

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